Annals of Clinical and Analytical Medicine
Original Research

Evaluation of the effect of coronary slow flow phenomenon on cardiac functions

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This study was presented as an 'poster presentation' at the 37th Turkish Cardiology Congress with International Participation, Antalya, Turkey, 2021

Abstract

Aim: Although coronary slow flow phenomenon (CSFP) is seen in 2% of patients undergoing coronary angiography, its clinical significance and impact on ventricular function remain controversial. Cardiac magnetic resonance imaging (CMR) is the gold standard for evaluating ventricular function and volumes. In this study, we aimed to assess the impact of CSF on ventricular function using CMR-based deformation imaging.

Material and Methods: This is a cross-sectional study. Twenty-two people were included in the study. Patients with structural heart disease and secondary coronary slow flow were excluded. Twelve subjects with CSFP and 10 subjects with normal flow and normal cardiac function were compared by CMR and CMR strain.

Results: Left ventricle (LV) and right ventricle (RV) functions and volumes were similar. There was no difference between CMR strains in both groups. Furthermore, there was no correlation between age and heart function in patients with CSF.

Discussion: CSF has no or limited impact on cardiac functions. Further long-term prospective studies should be carried out to establish the impact and significance of CSF in patients with CSF.

Keywords

Slow Flow, Strain, Atherosclerosis, Coronary Angiography

DOI: 10.4328/ACAM.21222 Received: 2022-05-10 Accepted: 2022-06-20 Published Online: 2022-06-23 Printed: 2022-10-01 Ann Clin Anal Med 2022;13(10):1098-1102
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Introduction

Coronary slow flow (CSF) is a rare angiographic clinical entity characterized by delayed distal vascular opacification without critical coronary artery stenosis. Microvascular disease has been proposed as a potential pathophysiological mechanism for this angiographic phenomenon and clinical findings [1].

Its incidence was reported to be 2% in patients undergoing coronary angiography. Although various mechanisms have been proposed for the pathogenesis of CSF, the underlying pathophysiology and clinical consequences of CSF are not clearly understood. A study supporting this hypothesis showed histologically small vessel coronary artery disease, myofiber hypertrophy, hyperplastic fibromuscular thickening of small arteries, swelling of endothelial cells, and narrowing of the lumen [2-5].

Similarly, some studies have suggested that CSF is associated with atherosclerosis and even has an early phase, which is only characterized by abnormal resistance of both small vessels and epicardial arteries [6].

However, another study proposed that improper release of vasoconstrictor autacoids such as neuropeptide Y, endothelin-1, and thromboxane A2 could lead the CSF [7]. Despite numerous published papers on the CSF, its clinical significance is still unclear, and the effects of CSF and subsequent inadequate blood supply on myocardial functions are still controversial. Comparative cross-sectional studies with different echocardiographic methods showed signs of early cardiac dysfunction in patients with CSF, but in these studies, conventional echo parameters were similar [8,9].

Cardiac magnetic resonance imaging (CMR) is the gold standard imaging method for ventricular functional assessment. Additionally, a new tool CMR-based deformation imaging 'Magnetic resonance imaging (MRI) tissue tracking', facilitates objective detection of wall motion abnormality. In this stuy, we aimed to perform a detailed assessment of the impact of CSF on cardiac function.

Material and Methods

Patient group and study protocol

Catheter laboratory records over the last year were evaluated to identify patients with CSF, and a total of 44 patients were detected. CSF can be a secondary related to many reasons. In our study, we excluded patients with CSF due to secondary reasons. In addition, we excluded patients with other conditions that could affect cardiac functions. Subjects who had structural cardiovascular disease (e.g., Left ventricle (LV) dysfunction, LV hypertrophy, cardiomyopathies, and atherosclerotic coronary artery disease), atrial fibrillation, valvular heart disease, congenital heart disease, pericardial disease, or stage 3– 4 hypertension were excluded from the study. Patients who had a bundle branch block on electrocardiogram, history of previous thoracic surgery, chronic systemic or inflammatory diseases, any form of malignancy and any contraindication to CMR imaging were excluded from the study as well. Finally, 12 patients, aged 24– 60 years were recruited into the study. Ten patients with normal coronary angiography and normal cardiac functions who agreed to participate in the study were enrolled as the control group. This study was approved by the local ethics committee of our hospital and was conducted in accordance with the principles outlined in the Declaration of Helsinki (Protocol no: 2020/05). Informed consent was obtained from all patients enrolled in the study.

TIMI frame count and definition of coronary slow flow

Thrombolysis in Myocardial Infarction (TIMI) frame count method explained by Gibson et al. was used to diagnose CSF. TIMI frame counts were measured by a cardiologist who was blinded to the properties of the patient. In this method, the first frame is formed at the first moment when the opaque matter begins to load in the ostium of the coronary artery. The last frame is decided at the moment when the first bifurcation in the posterior branch of the right coronary artery (RCA) is filled, and the first moment of opacification in the distal bifurcation for the circumflex (Cx) artery and left anterior descending (LAD) artery. Normal valuations when the frame rate of the coronary angiography machine is 30 frames/sec are 20.4±3.0 for RCA, 22.2±4.1 for Cx, and 36±2.6 for LAD. The corrected-LAD (cLAD) value is estimated by dividing the calculated value by 1.7, and the normal valuation for cLAD is 21.1±1.5. The mean TIMI frame count was estimated by adding these three valuations and dividing them by three. Patients with CSF in at least one of the three major coronary arteries were enrolled in the CSF group [10].

CMR protocol

Cine images and LV and RV functional measurement

All patients underwent CMR in a supine position in a 1.5 Tesla MRI scanner (GE Signa Medical Systems). Cardiac gating and triggering were performed via a vector ECG trace triggered on the R wave. The position of the heart was determined by a fast multi-slice, multi-stack survey scan in the transverse, coronal and sagittal planes. Scout imaging trans-axial, coronal, sagittal, these are in general single heartbeat acquisitions acquired in 1 breath-hold. After positioning of the heart in 3 planes, 4 chambers (CH), 2 CH, 3 CH, and short-axis cine stack with 10–12 slices were acquired with a steady-state free precession pulse sequence. The short axis stack covers from base to apex. Each slice location was acquired during breath holding during end-expiration. The shim volume feature was used for optimal image quality.

Placement Long axis images were used for quantitative LV functional assessment using tissue tracking tool. Short axis images were used. LV and right ventricle (RV) volume and ejection fraction measurement Cine images were acquired during a breath-hold. Slice thickness was 6–8 mm, with or without 2–4 mm interslice gaps (to make a total of 10 mm). Temporal resolution was ≤45ms between phases to optimize the evaluation of wall motion. Cardiac functional and volumetric measurements were performed using Circle CVI 42. Left ventricular ejection fraction (LVEF) and right ventricular Ejection fraction (RVEF) were measured from the short-axis cine stack according to the SCMR guideline [11].

Tissue tracking

CMR-based deformation assessment was done using long axis cine images. LV wall motions were assessed in 4 CH 3 CH and 2 CH long axis cine planes were analyzed by an experienced reader using Circle CVI 42 tissue tracking tool. Long axis endocardial and epicardial contours are required in end-diastole for tissue

tracking analysis. For the LV, these contours should be traced excluding the papillary muscle and trabeculations in the 2, 3, 4 CH image series. Endocardial contour detection was performed manually on long axis cine images in end-diastolic and and-systolic phases. After tracing the LV endocardial contours, LV long extent border indicator was checked and corrected if needed throughout all cardiac cycles (Figure 1). Global strain values including longitudinal (GLS) and radial LV strain (GRS) parameters were measured.

Statistical analysis

Data were expressed as mean ± standard deviation or as a percentage (number).

The Shapiro-Wilk test was used to evaluate the distribution of continuous variables. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as percentages and numbers. The t-test was used to compare normally distributed data. Categorical data were compared with the chi-square test or Fisher's exact test. Correlation analysis was done with Spearman rank correlation analysis. IBM SPSS Statistics 21 package program was used for data analysis. p <0.05 was accepted as the level of significance.

Results

There were 12 patients with CSF and 10 patients in the control group. An example of tissue tracking in CMR is shown in Figure 1.

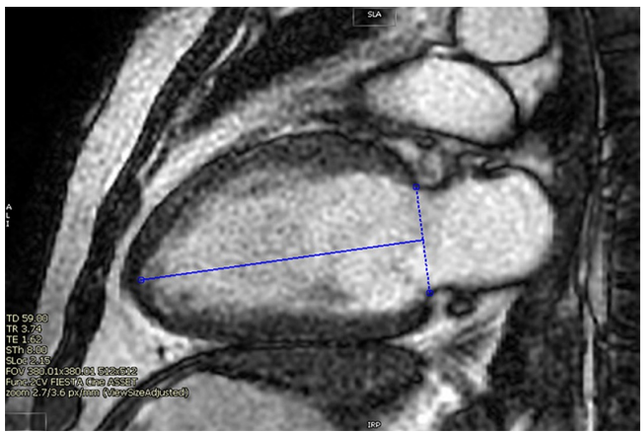

Figure 1. Tissue tracking in CMR

Table 1. TIMI frame count of patients with CSF

Patient	RCA	CX	LAD	cLAD	Mean TIMI	Gender
P1	28	28	42	24.71	26.90	Male
P2	30	38	50	29.41	32.47	Male
P3	20	32	38	22.35	24.78	Male
P4	24	28	40	23.53	25.18	Male
P5	24	28	42	24.71	25.57	Male
P6	28	34	48	28.24	30.Ağu	Male
P7	28	36	50	29.41	31.14	Male
P8	28	32	48	28.24	29.41	Female
P9	24	36	46	27.Haz	29.02	Female
P10	20	20	40	23.53	21.18	Female
P11	26	28	40	23.53	25.84	Female
P12	24	24	44	25.88	24.63	Female

TIMI: Thrombolysis in Myocardial Infarction, P: Patients, RCA: Right coronary artery, LAD: Left anterior descending artery, CX: Circumflex artery, cLAD: corrected Left anterior descending artery

Table 2. General characteristics, ventricular volumes and function of study population

Variables	CSF group (n=12)	Control group (n=10)	p value
Age (years)	52.50 ± 9.11	50.60 ± 5.08	0.564
Gender/Male (%/n)	66.7 (8)	70.0 (7)	1.000
BMI (kg/m2)	30.00 ± 4.84	30.32 ± 3.57	0.865
Systolic Blood Pressure (mmHg)	127.92 ± 13.56	130.50 ± 11.41	0.638
Diastolic Blood Pressure (mmHg)	79.58 ± 6.89	79.50 ± 7.25	0.978
Heart rate (beats/mn)	72.33± 7.74	69.70 ± 9.14	0.472
Smoking % (n)	58.3 (7)	50.0 (5)	1.000
Alcohol % (n)	41.7 (5)	40.0 (4)	1.000
Hypertension % (n)	41.7 (5)	50.0 (5)	1.000
Diabetes mellitus % (n)	25.0 (3)	30.0 (3)	1.000
Hyperlipidemia % (n)	50.0 (6)	50.0 (5)	1.000
Ventricular volumes and function			
LV EDV (ml)	142.17 ±31.97	157.00 ±34.40	0.308
LV ESV (ml)	57.67 ±16.95	60.40 ±25.48	0.767
LV EF (%)	59.58 ±5.93	60.90 ±8.29	0.669
RV EDV (ml)	139.17 ±34.78	156.20 ±32.00	0.250
RV ESV (ml)	62.50 ±16.27	65.40 ±14.61	0.668
RV EF (%)	54.92 ±5.62	57.00 ±9.08	0.537

CSF: Coronary slow flow, BMI: Body mass index, BSA: Body surface area, LV: Left ventricle, EDV: End diastolic volume, ESC: End systolic volume, SV: Stroke volume, EF: Ejection fraction, RV: Right ventricle

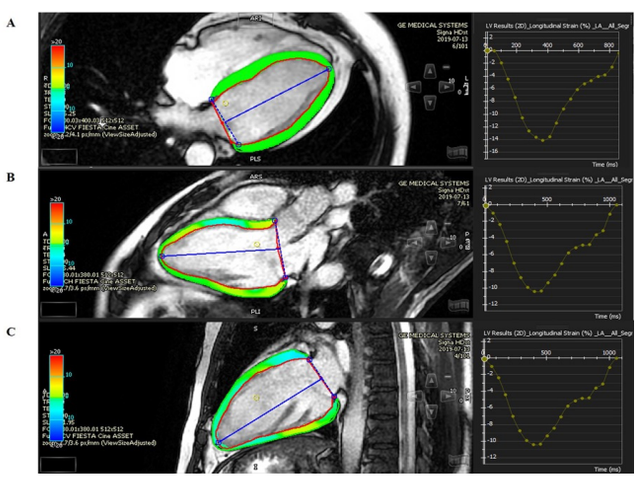

Figure 2. CMR-based deformation imaging for assessing wall movements. CMR-based deformation imaging for assessing wall motions is shown in Figure 2. Wall motions were assessed using the tissue tracking module. CMR strain parameters, including longitudinal and radial strain were similar in both groups (p > 0.05) (Table 3). There was no correlation between age and heart function in patient with CSF (p > 0.05).

Table 3. Cardiac MRI strain parameters

Variables	CSF group (n=12)	Control group (n=10)	p value
Global longitudinal strain	-12.65 ± 1.95	-13.14 ± 2.65	0.631
4 CH longitudinal strain	-12.78 ± 2.53	-13.19 ± 3.02	0.729
3 CH longitudinal strain	-12.73 ± 2.20	-12.43 ± 3.33	0.812
2 CH longitudinal strain	-11.82 ± 1.61	-13.64 ± 3.64	0.138
Global Radial Strain	19.40 ± 4.21	19.92 ± 5.88	0.819

MRI: Magnetic resonance imaging, CSF: Coronary slow flow, CH: Chamber

The average number of the TIMI frame count is shown in Table 1. The general characteristics, ventricular volumes and function of the study population were similar as depicted in Table 2. CMR parameters of the CSF group were compared with the control group. All volumetric parameters, masses, LVEF and RVEF were found to be similar in both groups ($p > 0.05$) (Table 2).

Discussion

In this study, we demonstrated that there is no statistically significant difference between patients with CSF and the normal population in terms of ventricular volumes and ventricular systolic function. In addition, left ventricular longitudinal strains were statistically similar in our study. Also, all values remained within the normal limits. To the best of our knowledge, this is the first detailed CMR study regarding CSF.

Only in a recently published study, the relationship between scar tissue and NT-proBNP was investigated in patients with CSF, but in this study, ventricular functions and volumes were not evaluated [12]. Early ventricular dysfunction was evaluated by various echocardiographic methods in patients with CSF. Although tissue Doppler parameters are lower, LVEF were statistically similar, and mean LVEF was higher than 60% in patients with CSF in previous echocardiographic studies with tissue Doppler [13]. LV strain, which is a more objective and sensitive tool for early identification of ventricular dysfunction, was found to be statistically lower than the normal population in various echocardiographic studies [14]. However, being statistically lower, LV strain values were still within normal limits in all these previous studies. Similarly, ventricular functions of patients were statistically similar in these studies, and the mean LVEF was over 60%.

The superiority of cardiac MR, which is the gold standard imaging modality for ventricular function and volume evaluation, has already been proven. In our study, CMR was used to assess ventricular volumes and functions, whereas CMR based deformation imaging was utilized to evaluate wall motions in a more detailed and objective way (Figure 2). A lot of mechanisms leading to CSF were accused, therefore some pathophysiological mechanism could be more detrimental than others. Of course, all these mentioned studies, including our study are cross-sectional. We thought that the exposure time of CSF could be important for ventricular functions, but there is no correlation between age and ventricular functions in patients with CSF. In addition, there was no negative correlation between the severity of coronary slow flow and ventricular functions. Also, different clinical presentations have also been reported in patients with CSF. CSF has been shown to cause chest pain, myocardial ischemia, prolonged QT interval in various publications. CSF has been reported to rarely cause arrhythmia and sudden death [15-17].

The commonest presentation of CSF was ACS (65%) requiring hospitalization. Mortality was not detected in these CSF patients presenting as an acute coronary syndrome. Different mechanisms have been claimed for CSF, so these different pathogeneses could lead to a heterogeneous effect and heterogeneous presentations. All patients were managed conservatively. As a result, it was concluded that CSF contributes to significant morbidity [18,19].

Although CSF is seen in 2 % of cardiac catheterizations, there is no guideline for the treatment of CSF phenomenon. Also, despite the fact that there are cross-sectional studies on the clinical effect of CSF, there is no long-term clinical follow-up study on CSF. In only one clinical follow-up study about angina and normal epicardial coronary arteries, 21 patients had slow coronary flow. They found that all patients had a good prognosis. In short-term follow-up studies, the treatment efficacy of some medications for symptoms was tested or coronary flow was re-evaluated after treatment. However, ventricular functions have not been evaluated. In addition, symptoms have been shown to be relieved with various medical treatments [20-24].

We speculate that impaired coronary perfusion pressure may cause angina. However, ventricular functions may be preserved because this perfusion pressure disorder is short-lived or coronary slow flow does not impair the basic supply of the ventricle in patients with CSF.

Limitations

Nonetheless, these results must be interpreted with caution and a number of limitations should be borne in mind. The first is the small sample size of our population due to the strict inclusion and exclusion criteria. The second major limitation concerns the unknown exact duration of CSF exposure. Because of local ethic committee disallowance regarding contrast use, we were solely able to use conventional volume and function assessment. As regards wall motion evaluation, tissue tracking tools were utilized. Nevertheless, this is a cross sectional study and the results clearly indicates the relationship, and there is an apparent need for a prospective follow-up study.

Conclusion

As a result of all, we concluded that CSF has no or limited impact on the ventricular volumes and functions. There is no established treatment protocol for CSF and it is generally assumed to have benign long-term outcomes. However, further long-term prospective studies should be carried out to establish the impact and significance of CSF on cardiac volumes and functions.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:
Ahmet Barutcu, Ercan Akşit, Mehmet Arslan, Özge Özden Tok, Uğur Küçük. Evaluation of the effect of coronary slow flow phenomenon on cardiac functions. Ann Clin Anal Med 2022;13(10):1098-1102